IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Examiner	: Darryl C. Sutton	
Serial No.	: 10/501,692	
Filed	: July 15, 2004	Docket No.: END-04-1182PCT-US
Inventors	: Richard Smith-Carliss	
	: Frank S. Caruso	
	: Peter A. Crooks	
	: Kenneth J. Kellar	Confirmation No.: 4419
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Title	: ANALGESICS AND METHODS	
	: OF USE	
		Dated: November 19, 2008

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The Appellants have appealed from the rejection of Claims 23-26, 28-30, 33 and 34. The Appellants submit this Appeal Brief in response to the Official Action dated June 25, 2008. The Appellants submit electronic payment in the amount of $510.00 under 41 CFR §41.20(b)(2). The Commissioner is authorized to charge any insufficiency to Deposit Account No. 50-2719.

REAL PARTY IN INTEREST

The real party in interest by Assignment recorded in the USPTO records at Reel 015743 and Frame 0001 is Endo Pharmaceuticals, Inc., a corporation of Delaware, located at 100 Endo Boulevard, Chadds Ford, PA 19317.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

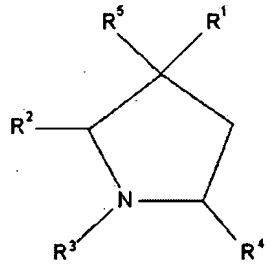
The Appellants' Claims 1-22 were cancelled without prejudice and without disclaimer of the subject matter thereof. Claims 23-26, 28-30, 33 and 34 are rejected and are on appeal. Claim 23 is an independent claim.

STATUS OF THE AMENDMENTS

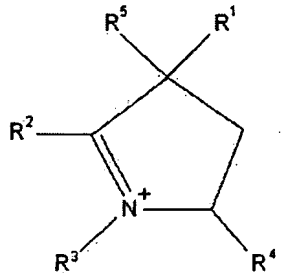
The following Response is of record: A Response filed January 25, 2008 in response to the non-final Official Action dated July 26, 2007; and a Notice of Appeal filed August 5, 2008 in response to the final Official Action dated June 25, 2008. A copy of the claims as they now stand is provided in the Claims Appendix. No amendment has been filed subsequent to the final Official Action.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter in independent Claim 23 relates to a pharmaceutical composition comprising a pharmaceutically acceptable agent; and a compound selected from one of Formula I and Formula II, and pharmaceutically acceptable salts thereof:



Formula I



Formula II

where Formulas I and II include all possible geometric, racemic, diasteriomeric, and enantiomeric forms and where R^1 is selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkenyl, aryl and azaaromatic; R^2 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkene, and $(C_2\text{-}C_6)$alkynyl, and in Formula I, R^2 may additionally be selected from O= or HN=; R^3 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, aryl, and aryl$(C_1\text{-}C_6)$alkyl; and R^4 is $(C_1\text{-}C_6)$alkyl, and $(C_3\text{-}C_6)$cycloalkyl; and R^5 is aryl or azaaromatic and may form a bond to R^1 to result in a conjugated ring system; in an amount sufficient to induce analgesia and/or deter abuse of abusive substances. *See* the Specification at page 12, at lines 13-29; at page 13, at

lines 1-35; at page 14, at lines 1-3; the Table beginning at page 14, at line 4 and continuing though page 20 at line 1; at page 20, at lines 4-5; at page 21, lines 1-30; at page 22, at lines 1-26; at page 24, at lines 23-35; at page 25, at lines 1-35; at page 26, lines 1-11; at Figure 1; at Figure 8; and at Figure 9.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 23-26, 28-30, 33 and 34 are rejected under 35 USC §103(a) over Angelo (724 J. Chromatography B 35 (1999)).

ARGUMENT

Rejection of Claims 23-26, 28-30, 33 and 34 under 35 USC §103(a)

The Appellants respectfully submit that Claims 23-26, 28-30, 33 and 34 are not obvious under 35 USC §103(a) over Angelo. There are several reasons for this. First, Angelo fails to disclose, teach or suggest all the elements of Claims 23-26, 28-30, 33 and 34. Second, one of ordinary skill in the art would not be motivated to make a pharmaceutical composition given the teachings of Angelo. Third, one of ordinary skill in the art would not reasonably expect to successfully make the claimed pharmaceutical composition, which is capable of inducing analgesia and aiding in drug deterrence therapy, based on the teachings of Angelo.

Failure of Angelo to Teach All the Elements of the Claims

The Appellants respectfully submit that Claims 23-26, 28-30, 33 and 34 are not obvious under 35 USC §103(a) over Angelo because Angelo fails to teach all the elements of the pharmaceutical compositions of these claims. Independent claim 23 is directed to a "pharmaceutical composition" comprising a "pharmaceutically acceptable agent" and "a compound selected from one of Formula I or II" such as 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). Claims 24-26, 28-30, 33 and 34 are dependent on independent Claim 23 and incorporate all of its recitations. Angelo does not teach a pharmaceutical composition comprising a pharmaceutically acceptable agent and a compound of Formula I or II such as EDDP. Instead, Angelo only teaches two categories of compositions that comprise EDDP perchlorate salt and none of the compositions in those categories comprise a "pharmaceutical acceptable agent" or are otherwise pharmaceutically acceptable.

The first category of such compositions is "stock standard solutions" which comprise EDDP perchlorate from Sigma-Aldrich Co. (St. Louis, MO), (+)-(*R*)-EDDP perchlorate salt from NTI Intl. (Research Triangle Park, NC), or (-)-(*S*)-EDDP perchlorate salt from NTI Intl. (Research Triangle Park, NC) in "analytical-reagent grade" ethanol. The second category of such compositions is "calibration samples" comprising these "stock standards" in "blank urine" from human volunteers who apparently are known not to have received methadone, EDDP or any other methadone metabolites.

Importantly, the EDDP perchlorate available from Sigma-Aldrich Co. is minimally 98% pure and not a USP (United States Pharmacopeia-National Formulary) grade compound, or other compound grade suitable for use in a pharmacological composition. Similarly, the (+)-(*R*)-EDDP perchlorate salt and the (-)-(*S*)-EDDP perchlorate salt from NTI Intl. (Research Triangle Park, NC) are of unknown purity and are not taught to be USP grade compounds or other compound grades suitable for use in a pharmacological composition. Additionally, the "analytical-reagent grade" ethanol used is of unknown purity and clearly not a USP grade compound or other compound grade and is not a "pharmaceutically acceptable agent" suitable for use in a pharmacological composition. Last, the compositions comprising "blank urine" from humans and the EDDP compounds described above are clearly not suitable for use in a pharmacological composition. Consequently, Angelo fails to teach all the elements of the claims because it does not teach a pharmaceutical composition comprising a "pharmaceutically acceptable agent" such as a pharmaceutically acceptable carrier.

This is not surprising considering that Angelo does not teach a biological activity for EDDP or any of the methadone metabolites examined and, instead, only made compositions intended for use in the context of chromatographic analyses. This context further clarifies that the compositions taught in Angelo are not pharmaceutical compositions to be administered to patients and that Angelo fails to teach all the elements of claims 23-26, 28-30, 33 and 34.

Failure of Angelo to Establish Motivation for One of Ordinary Skill in the Art

The Appellants respectfully submit that Claims 23-26, 28-30, 33 and 34 are not obvious under 35 USC §103(a) over Angelo because one of ordinary skill in the art would not be motivated to make a pharmaceutical composition given the teachings of Angelo. Reasons are set forth below.

First, Angelo would not motivate one of ordinary skill in the art to make the claimed pharmaceutical compositions because Angelo is silent as to potential biological activity of EDDP. Instead, Angelo teaches a chromatographic method for resolving and detecting stereoisomers of methadone and the primary metabolite of methadone called EDDP. Importantly, Angelo discloses nothing concerning potential biological activity of EDDP and is only concerned with developing chromatographic methods for resolving the stereoisomers of methadone and its metabolites. In fact, the compositions and methods of Angelo were only for "the purpose of examining the stereoselectivity of the metabolism of methadone[.]" *See* Angelo at 36.

In other words, Angelo does not teach that EDDP and the other compounds of Formulas I and II have any biological activity or could provide analgesia or drug deterrence in a pharmaceutical composition. Consequently, one of ordinary skill in the art would not be motivated to make the claimed pharmaceutical compositions comprising the compounds of Formulas I and II, such as EDDP, and a "pharmaceutically acceptable agent[,]" such as a pharmaceutically acceptable carrier.

Second, Angelo would not motivate one of ordinary skill in the art to make the claimed pharmaceutical compositions because it is entirely unreasonable to expect that the main metabolite of a drug, such as methadone, will automatically have the properties of the drug from which it is formed even though the metabolite has a very different chemical structure. The rejection, however, relies on such an unreasonable expectation to establish motivation and states in part that "since methadone induces analgesia and aids in drug deterrence..., one skilled in the art would reasonably expect that similar properties would be found in the main metabolite of methadone."

It is worth noting that Angelo teaches the different metabolites of methadone, including EDDP, are formed in part by progressive *N*-demethylation. This means that one of ordinary skill in the art would recognize that a variety of different methadone metabolites are formed during the progressive metabolism of this drug. Additionally, one of ordinary skill in the art would recognize that each of these different metabolites would have different chemical structures and physical properties distinct from those of the drug from which these degradation products were formed.

However, one of ordinary skill in the art simply would not conclude that, just because a particular metabolite is the main metabolite of a drug, it will automatically have the same properties as that drug. This is because metabolites are structurally distinct drug degradation products that may be biologically inactive or even toxic and it is extremely difficult to predict based solely on the

prevalence of a metabolite, or even just the structure of such a compound, whether it will have particular physical properties or biological activities.

In fact, the Appellants respectfully submit that much of modern drug discovery would be entirely unnecessary if such a high level of predictability existed in the identification of biologically active compounds suitable for use in pharmaceutical compositions. Unfortunately, this is simply not the case and one of ordinary skill in this unpredicatable art would not be motivated to make a pharmaceutical composition given the teachings of Angelo because they would have no knowledge or expectation that the EDDP stereoisomers resolved by chromatography would be biologically active. Stated differently, without knowledge a molecule has a particular property, one of ordinary skill in the art would not be motivated to make a pharmaceutical composition utilizing this property to produce a biological effect.

A simple example showing that it is unreasonable to expect the main metabolites of a drug to have the same biological activity as the drug is provided by examining the metabolism of ethanol. Ethanol (perhaps one of the oldest and most familiar drugs known) is metabolized in the human body to acetic acid and acetaldehyde. However, it is well known that the biological effects of ethanol are not due to either of these metabolites and the administration of these metabolites does not produce the same effects as ethanol. Acetaldehyde, for example, is toxic and has been linked to cirrhosis of the liver and certain forms of cancer. Acetic acid can disrupt the control of pH within cells and can produce toxic effects through such disruption and the denaturation of proteins. This example, and the many others like it, make clear the unpredictability of drug metabolism and the inability of one of ordinary skill in the art to predict whether metabolites will have the same biological activity as the drug from which these degradation products were formed. Stated differently, this example shows why one of ordinary skill in the art simply cannot predict, and would not conclude, that because a particular metabolite is the main metabolite of a drug, it will automatically have the same properties as that drug.

Third, the rejection fails to establish Angelo would motivate one of ordinary skill in the art to make the claimed pharmaceutical compositions because it relies on properties inherent to EDDP. The rejection states that "all the physical properties and activities of the compound, and therefore the composition, are inherent to the structure of the compound." In other words, the rejection acknowledges that Angelo does not expressly teach that EDDP and the other compounds of

Formulas I and II have any biological activity or could provide analgesia or drug deterrence in a pharmaceutical composition. Moreover, it is self evident to state:

> "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *See* In re Spormann and Heinke, 150 USPQ 499, 452 (CCPA 1996) (emphasis added).

This means the rejection fails to establish that Angelo would motivate one of ordinary skill in the art to make the claimed pharmaceutical compositions. This is because a person of ordinary skill in the art simply would not have known, based on Angelo that compounds of Formulas I and II, such as EDDP, could be at all useful in a pharmaceutical composition and, consequently, would not have been motivated to make such a pharmaceutical composition. Furthermore, as discussed above, Angelo fails to even disclose any pharmaceutical compositions.

Fourth, the rejection improperly relies on In re Adamson to help establish motivation. *See* In re Adamson, 125 USPQ 233 (CCPA 1960) (hereinafter "Adamson"). The rejection cites In re Adamson for the propositions that the existence of a racemate is sufficient to render obvious any individual stereoisomers present in the racemate and that one skilled in the art expects individual stereoisomers will differ in physiological activity, pharmacological activity, and toxicity. In Adamson an individual stereoisomer isolated from a prior art racemate was claimed by the Appellant. *See* Adamson at 233. One prior art publication cited in Adamson taught a racemate comprising the claimed stereoisomer and apparently also taught that it was known that the racemate was biologically active as a muscle relaxant. *See* Adamson at 234. A second prior art publication cited in Adamson taught that individual stereoisomers in racemates could be isolated by various methods that included the one utilized by the Adamson Appellant. *See* Adamson at 234. In reaching the conclusion of obviousness, the Adamson court acknowledged at least one of the stereoisomers present in the prior art racemate had to be responsible for the known muscle relaxant activity of the prior art racemate, and that there was nothing unexpected about the fact that the stereoisomer with muscle relaxant activity had been isolated from this racemate using known methods for isolating stereoisomers. *See* In re Adamson at 235; *see also* Aventis Pharma Deutschland GmbH v. Lupin, Ltd. 499 F.3d 1293, 1301 (Fed. Cir. 2007) (clarifying that the holding of obviousness in Adamson was due to "insufficient showing of unexpected result."); *see also* Sanofi-Synthelabo v. Apotex, Inc.

470 F.3d 1368, 1380 (Fed. Cir. 2006) (distinguishing Adamson based on a showing of unexpected results).

Adamson is inapplicable here for several different reasons. The primary reason is that what is claimed here is not an individual stereoisomer, but instead pharmaceutical compositions comprising a "pharmaceutically acceptable agent," such as a carrier, and the compounds of Formulas I and II, such as EDDP. As discussed above, such a pharmaceutical composition would have been entirely unexpected because EDDP and similar compound had no known biological activity prior to the Appellants' discovery of the analgesic and drug deterrence properties of these compounds. Furthermore, Angelo teaches no biological activity for EDDP or similar compounds.

Fifth, the rejection fails to establish that Angelo would motivate one of ordinary skill in the art to make the claimed compositions because Angelo teaches away from pharmaceutical compositions. It is well settled that the prior art must be considered as a whole for all that it teaches including disclosures that "teach away from the claimed invention." *See e.g.* W. L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983). In the context of this rejection, this means all the teachings of Angelo must be considered. As discussed above Angelo was concerned with the development of methods and compositions useful for chromatographically resolving and detecting stereoisomers of methadone and the metabolite EDDP. Furthermore, only "calibration samples" and "stock standards" using analytical or reagent grade compounds are prepared for use in these chromatographic analyses. Taken together, it can be seen that the teachings of Angelo would, at best, cause a person of ordinary skill to be motivated to make compositions suitable only for chromatography, not pharmaceutical compositions for administration to a patient.

Failure of Angelo to Establish Reasonable Expectation of Success for One of Ordinary Skill in the Art

The Appellants respectfully submit that Claims 23-26, 28-30, 33 and 34 are not obvious under 35 USC §103(a) over Angelo because one of ordinary skill in the art would not have a reasonable expectation of successfully making a pharmaceutical composition given the teachings of Angelo. This is because as discussed above:

1) Angelo fails to teach all elements of the pharmaceutical compositions of the claims.
2) Angelo is silent as to potential biological activity of EDDP.

3) It is entirely unreasonable to expect that the main metabolite of a drug, such as methadone, will automatically have the properties of the drug from which it is formed.
4) The rejection relies on inherent disclosure and properties inherent to EDDP.
5) The rejection improperly relies on In re Adamson.
6) Angelo teaches away from pharmaceutical compositions.

The cumulative effect of these shortcomings is that one of ordinary skill in the art could not reasonably expect to successfully make the claimed compositions based on the teachings of Angelo.

Unexpected Results

The Appellants respectfully submit that Claims 23-26, 28-30, 33 and 34 are not obvious under 35 USC §103(a) over Angelo because the Appellants discovered that the claimed pharmaceutical compositions produce unexpected results. The Appellants' experiments unexpectedly discovered that EDDP has different physiological functions than (-)-(*R*)-methadone which is both a μ-opioid receptor agonist and a NMDA (N-methyl-D-aspartate) receptor ion channel antagonist capable of blocking MK-801 (also known as dizocilpine, a non-competitive antagonist of the NMDA receptor that produces anesthetic and anti-convulsant effects) binding to the NMDA receptor. For example, the specification shows that only 10 μM of methadone or MK-801 are required to block catecholamine release mediated by the NMDA receptor, whereas 100 μM of EDDP is required to have any effect. *See e.g.* the Specification at page 4, at lines 20-32; and Figures 13 and 14. In contrast, EDDP affects nicotinic acetylcholine receptors (nAchR), such as the α3β4 nAChR, with five times the potency of methadone. The different inhibitory concentrations of these compounds for different receptor molecules indicates that EDDP has a distinct and entirely unexpected biological function from the parent molecule. In contrast, Angelo fails to teach any biological activity for EDDP as discussed above. Therefore, the Appellants respectfully submit that one of ordinary skill in the art, in view of Angelo, could not have predicted a composition comprising EDDP would act on nicotinic receptors to induce analgesia and deter drug abuse. In other words, the Appellants' discovery of a pharmaceutical composition comprising the compounds of Formulas I and II, such as EDDP, which mediates its effects through nicotinic acetylcholine receptors (nAchR), such as the α3β4 nAChR, is entirely unexpected and not obvious.

In light of the foregoing, the Appellants respectfully request that the rejection of Claims 23-26, 28-30, 33 and 34 accordingly be reversed.

Respectfully submitted,

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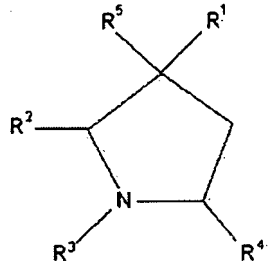
Claim Appendix

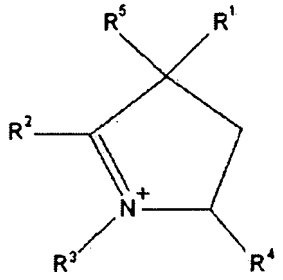
23. A pharmaceutical composition comprising:

a pharmaceutically acceptable agent; and

a compound selected from one of Formula I and Formula II, and pharmaceutically acceptable salts thereof:



Formula I



Formula II

where Formulas I and II include all possible geometric, racemic, diasteriomeric, and enantiomeric forms and where:

R^1 is selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl-$(C_1\text{-}C_6)$alkenyl, aryl and azaaromatic;

R^2 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkene, and $(C_2\text{-}C_6)$alkynyl, and in Formula I, R^2 may additionally be selected from O= or HN=;

R^3 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, aryl, and aryl$(C_1\text{-}C_6)$alkyl; and

R^4 is $(C_1\text{-}C_6)$alkyl, and $(C_3\text{-}C_6)$cycloalkyl; and R^5 is aryl or azaaromatic and may form a bond to R^1 to result in a conjugated ring system;

in an amount sufficient to induce analgesia and/or deter abuse of abusive substances.

24. The composition of claim 23, wherein R^1 is selected from the group consisting of aryl and azaaromatic, each having 1-5 substituents independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, N-methylamino, N,N-dimethylamino, carboxylate, $(C_1\text{-}C_3)$alkylcarboxylate, carboxaldehyde, acetoxy, propionyloxy, isopropionyloxy, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, carboxamide, N-methylcarboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, thiol, methylthio, ethylthio,

propiothiol, fluoro, chloro, bromo, iodo, trifluoromethyl, propargyl, nitro, carbamoyl, ureido, azido, isocyanate, thioisocyanate, hydroxylamino, and nitroso.

25. The composition of claim 23, wherein R^5 is selected from the group consisting of aryl and azaaromatic, each having 1-5 substituents independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, N-methylamino, N,N-dimethylamino, carboxylate, $(C_1\text{-}C_3)$alkylcarboxylate, carboxaldehyde, acetoxy, propionyloxy, isopropionyloxy, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, carboxamide, N-methylcarboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, thiol, methylthio, ethylthio, propiothiol, fluoro, chloro, bromo, iodo, trifluoromethyl, propargyl, nitro, carbamoyl, ureido, azido, isocyanate, thioisocyanate, hydroxylamino, and nitroso.

26. The composition of claim 23 wherein R^3 is methyl or ethyl.

28. The pharmaceutical composition according to claim 23, wherein said analogs are in the form of pharmaceutically acceptable salts.

29. The pharmaceutical composition of claim 28, wherein said pharmaceutically acceptable salts are inorganic acid addition salts, organic acid addition salts, salts with acidic amino acids, and hydrates or solvates thereof with alcohols and other solvents.

30. The pharmaceutical composition of claim 29, wherein said analog is an inorganic acid addition salt selected from the group consisting of hydrochloride, hydrobromide, sulfate, phosphate and nitrate.

33. The pharmaceutical composition of claim 23, wherein the composition blocks an nAChR.

34. The pharmaceutical composition of claim 31, wherein the nAChR is the $\alpha 3\beta 4$ receptor.

Evidence Appendix

No evidence is being submitted.

Related Proceedings Appendix

There are no related proceedings.